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Non-coding RNAs regulate tumor cell plasticity

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Tumor metastasis is one of the most serious challenges for human cancers as the majority of deaths caused by cancer are associated with metastasis, rather than the primary tumor. Recent studies have demonstrated that tumor cell plasticity plays a critical role in tumor metastasis by giving rise to various cell types which is necessary for tumor to invade adjacent tissues and form distant metastasis. These include differentiation of cancer stem cells (CSCs), or epithelial-mesenchymal transition (EMT) and its reverse process, mesenchymal-epithelial transition (MET). A growing body of evidence has demonstrated that the biology of tumor cell plasticity is tightly linked to functions of non-coding RNAs (ncRNAs), especially microRNAs (miRNAs) and long non-coding RNAs (lncRNAs). Therefore, understanding the mechanisms how non-coding RNAs regulate tumor cell plasticity is essential for discovery of new diagnostic markers and therapeutic targets to overcome metastasis.

metastasis, tumor cell plasticity, CSCs, EMT, miRNA, lncRNA

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Tumor cell plasticity describes the ability of tumor cells to transform into other cell types. This process generates cells with new phenotypes ensuring their proliferation and metastasis. Cancer stem cells (CSCs) are cancer cells that possess characteristics associated with normal stem cells, especially the ability to give rise to all cell types found in a particular tumor [1,2].

Epithelial-mesenchymal transition (EMT) is the process by which epithelial cells lose epithelial characteristics and gain mesenchymal characteristics. During EMT, epithelial cells lose cell-cell junctions, thus facilitating cell individualization. In addition, the epithelial apical-basal polarity is lost, and a complete reorganization of the actin cytoskeleton enhances cell locomotion along rear-to-front polarity. EMT also enables cells to acquire invasive properties, thus degrading extracellular matrix and re-synthesizing extracellular matrix proteins [3,4]. Transcription factors Snail (Snail/Slug), ZEB (ZEB1/ZEB2), and Twist1 act to repress E-cadherin expression, and induce mesenchymal gene expression, such as vimentin and fibronectin in this transition [5]. In carcinomas, cancer cells can undergo EMT to escape the primary tumor, invade surrounding tissues, and eventually colonize remote sites via blood or lymphatic routes to generate metastases. Metastatic cells can then revert through mesenchymal-epithelial transition (MET) to re-acquire epithelial characteristics similar to cells in the primary tumor.

Therefore, development of specific therapies targeted at CSCs and EMT holds hope for improvement of survival and quality of life of cancer patients, especially for sufferers of metastatic disease. The molecular and cellular mechanisms underlying CSCs and EMT are complex. The discovery that non-coding RNAs (ncRNAs) are powerful regulators of CSCs and EMT has added an important new layer to our understanding of tumor cell plasticity and the regulation of these processes in cancer.

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1 Classification of ncRNAs

Non-coding RNAs (ncRNAs) are RNA molecules that do not function by encoding for proteins. They are loosely grouped into two major classes based on their size: small ncRNAs less than 200 nt, and long ncRNAs (lncRNAs) longer than 200 nucleotides (nt) [6,7]. Small ncRNAs are represented by a broad range of known and newly discovered RNA species [8,9]. These include well-characterized housekeeping ncRNAs such as tRNA and rRNA which are essential for fundamental cellular functions, splicing RNAs (snRNAs) that regulates mRNA splicing, and a variety of recently-observed RNAs regulating transcription, such as tiny transcription-initiation RNAs, promoter-associated short RNAs and termini-associated short RNAs. However, the most extensively studied small RNAs in cancer are microRNAs (miRNAs) [6,7].

miRNAs are small double-strand RNAs at ~22 nt long. They regulate protein expression at post-transcriptional level by binding to the 3′UTRs of target mRNAs, which leads to translation repression or target mRNA cleavage [10,11]. miRNAs are grouped into families based on similarity of seed sequences. Members of a family are expected to have many overlapping targets. Therefore, individual miRNAs often target multiple mRNAs within a common pathway, increasing the robustness of their effects on cellular processes such as EMT, while single mRNAs can be regulated by multiple miRNAs [12].

In contrast to miRNAs, lncRNAs are mRNA-like transcripts ranging in length from 200 nt to ~100 kilobases (kb) lacking significant open reading frames. Many identified lncRNAs are transcribed by RNA polymerase II (RNA pol II) and are polyadenylated [13,14]. Transcription of lncRNAs occurs from an independent gene promoter and is not coupled to the transcription of a nearby or associated parental gene, as with promoter/termini associated RNAs [6]. Although only a minority have been characterized in detail, lncRNAs participate in diverse biological processes through distinct mechanisms. Generally, lncRNAs have been implicated in chromosome dosage-compensation, imprinting, epigenetic regulation, cell cycle control, nuclear and cytoplasmic trafficking, transcription, translation, splicing, cell differentiation, and others [15−19].

2 miRNA regulation of CSCs and EMT

Breast CSCs (BCSCs) were the first CSCs in solid tumors to be reported and are among the best characterized CSCs [20]. BCSCs can be enriched by consecutively passaging breast cancer cell SKBR3 in mice treated with chemotherapy [21]. These xenografts contain a high percentage of stem-like $CD44^+/CD24^-$ cells. Importantly, the BCSC-enriched cells expressed much lower levels of let-7 as well as a number of other miRNAs, including miR-16, miR-107, miR-128, and miR-20b, than the parental cells. let-7 regulated self-renewal and differentiation of BCSCs by targeting H-RAS and HMGA2, respectively. Overexpression of let-7a inhibited mammosphere formation, tumor formation, and metastasis in NOD/SCID mice and reduced the proportion of undifferentiated cells *in vitro*. Subsequently, miR-30 was also found to be markedly reduced in BCSCs and to negatively modulate the stemness of BCSCs. Overexpression of miR-30 in BCSCs not only diminished their self-renewal ability but also reduced anoikis resistance and increased apoptosis by targeting UBC9 and integrin β3. A more complete inhibition of self-renewal in BCSCs was observed when both let-7 and miR-30 were introduced at the same time, compared with transfecting either miRNA alone. The synergistic inhibitory effects of let-7 and miR-30 suggest that multiple miRNAs may distinctively and concertedly regulate CSC properties [22].

Furthermore, miR-17-19b is up-regulated in leukemia stem cells, consistent with reduced differentiation and increased proliferation, in part by modulating the expression of p21 [23]. miR-34a was found to be down-regulated in human glioblastomas. Transfection of miR-34a into glioblastoma multiforme (GBM) CSCs caused cell-cycle arrest or apoptosis and also inhibited xenograft growth, mediated by down-regulation of multiple oncogenic targets, including c-MET, Notch-1/2, and CDK6 [24]. The miR-181 is important for the maintenance of hepatic cancer stem cells by down-regulating two hepatic transcriptional regulators promoting differentiation (CDX2 and GATA6) and an inhibitor of Wnt/β-catenin signaling (NLK) [25].

Several miRNAs directly target families of EMT transcription factors. For example, the transcription factors ZEB1 and ZEB2 have been confirmed as targets of miR-200 family [26,27]. Conversely, ZEB1 represses the transcription of miR-200 genes by binding to their promoter region, thereby forming a double-negative feedback loop [28]. A striking negative correlation was found between ZEB and miR-200 expression in many human cancer cell lines. miR-205 was also reported to inhibit ZEB1 and ZEB2 expression [26]. Snail is targeted by miR-29b and miR-30a [29,30]. Accordingly, enhanced expression of miR-29b in metastatic prostate cancer cells reverses EMT and inhibits the invasive phenotype. Furthermore, miR-1 and miR-200b both directly target Slug in prostate adenocarcinoma cells [31]. In this system, TGF-β-induced EMT results in expression of Slug, which in turn transcriptionally represses the expression of both miR-1 and miR-200b, forming a double negative feedback loop. miR-200b and miR-15b were down-regulated in cisplatin-resistant tongue squamous cell carcinoma (TSCC) cells, which show the acquisition of EMT phenotype. Re-expression of miR-200b and miR-15b induced MET with up-regulated E-cadherin expression, down-regulated vimentin and fibronectin expressions, and inhibited invasion and migration in cisplatin-resistant cells

by targeting BMI1. *In vivo*, miR-200b or miR-15b suppressed metastasis of TSCC xenografts established by cisplatin-resistant cells [32].

Mani et al. [33] first firmly connected EMT and CSCs by inducing HMLE cells to undergo EMT by Snail or Twist and revealed that the EMT markers are highly expressed in human mammary CSCs that were $CD44^{high}/CD24^{low}$ and were able to form mammospheres. Subsequently, the connection of EMT and CSCs was demonstrated in many other human cancers. miR-21 acts as oncogenic miRNA, and its expression promotes EMT and CSC characteristics in breast cancer cells, notably through inhibition of PTEN expression [34,35]. Expression of the miR-106b-25 cluster, which acts downstream of the transcription factor Six1, induces EMT and tumor-initiating characteristics in human breast cancer cells, through direct repression of Smad7, thus increasing TGF-β signaling [36]. Linking EMT and CSCs to specific miRNAs will enable us to better understand how metastatic cancer arisen and targeting these regulatory miRNAs may provide new ways to overcome cancer.

3 lncRNAs in cancer

According to recent results from ENCODE project, 62% of human genome is coding for transcripts longer than 200 nt, yet only 5.5% of them is represented by coding exons. It is estimated that the total number of lncRNAs is between 10000 and 200000 [37]. However, only very few examples of lncRNAs have been functionally characterized [15,38]. Recent studies show that lncRNAs are exquisitely regulated during development and in response to diverse signaling cues, and can be misexpressed in solid tumors and leukemias [39], suggesting that lncRNAs constitute an important component of tumor biology. One of the first lncRNAs described to have fundamental roles in cancer was the HOX antisense intergenic RNA (HOTAIR), encoded by a 2.2 kb gene located in the mammalian HOXC locus on chromosome 12q13.13 [40]. This lncRNA was found to be highly up-regulated in both primary and metastatic breast tumors. High levels of HOTAIR expression were correlated with both metastasis and poor survival rate [41].

The MALAT1 gene, or metastasis-associated lung adenocarcinoma transcript 1, was first associated with high metastatic potential and poor patient prognosis during a comparative screen of non-small cell lung cancer patients with and without metastatic tumors [42]. Recently, Ying et al. [43] found that MALAT-1 levels were up-regulated in bladder cancer tissues compared with adjacent normal tissues, and siRNA-mediated MALAT-1 silencing resulted in a decrease of ZEB1, ZEB2 and Slug levels, and an increase of E-cadherin levels. MALAT-1 promoted EMT by activating Wnt signaling *in vitro*. These data suggest a potential application of MALAT-1 in cancer therapy.

Several lncRNAs are implicated in the regulation of p53 tumor suppressor signaling. MEG3, a maternally-expressed imprinted lncRNA on Chr14q32, has been shown to activate p53 and facilitate p53 signaling, including enhancing p53 binding to target gene promoters [44]. MEG3 overexpression suppresses cell proliferation in meningioma [45] and hepatocellular carcinoma cell lines [46]. A recently described murine lncRNA located near the p21 gene, termed linc-p21, has also emerged as a promising p53-pathway gene. In murine lung, sarcoma, and lymphoma tumors, linc-p21 expression is induced upon activation of p53 signaling and represses p53 target genes through a physical interaction with hnRNP-K, a protein that binds the promoters of genes involved in p53 signaling. linc-p21 is further required for proper apoptotic induction [47]. These two lncRNAs may be a putative tumor suppressor.

Recent research has shed light on the possibilities that lncRNAs could regulate crucial signal pathways in tumor cell biology. lncRNA low expression in tumor (lncRNA-LET) is down-regulated in hepatocellular carcinomas and other types of cancers. It is down-regulated by hypoxia-induced histone deacetylase 3, and down-regulation of lncRNA-LET enables stabilization of nuclear factor 90 protein, which leads to hypoxia-induced cell invasion [48]. Another study shows that two lncRNAs, PRNCR1 and PCGEM1, bind to androgen receptor and are required for ligand-dependent activation of androgen receptor pathway. Moreover, their pathological up-regulation can trigger ligand-independent activation of androgen receptor pathway and may facilitate castration resistance in prostatic tumors [49]. These examples have raised the possibility that lncRNAs may play significant roles in tumor cell plasticity by being involved in regulation of critical signal pathways.

4 Concluding remarks and future perspectives

Malignant tumors are heterogeneous in their cellular components. Tumor cells vary in their tumorigenicity, ability to metastasis, and resistance to therapies. This nature of tumor cells is governed by both genetic heterogeneity and cellular plasticity. Growing evidence suggests that cellular plasticity is tightly linked to tumor progression, metastasis, resistance to therapies, and relapse. Recent studies show non-coding RNAs played a critical role in regulating tumor cell plasticity. These mainly include miRNAs and lncRNAs, as they exert their functions by regulating gene expression which is essential mechanism of cell plasticity (Table 1). Future explorations of expressions and functions of these expression-regulating molecules in human cancer may lead to discoveries of new markers for diagnosis or developments of targeted therapeutics.

Challenges of analyzing functions of cancer related ncRNAs mainly involve specifically modulation of their expressions. While genetic knock-outs of certain protein-coding genes are often achieved by introducing a stop

Table 1 ncRNAs regulating tumor cell plasticity

ncRNA	Summary	Reference
miRNA		
let-7	Down-regulated in breast cancer stem cells, regulate breast cancer stem cell differentiation by targeting H-RAS and HMGA2	[21]
miR-30	Down-regulated in breast cancer stem cells, regulate self-renewal and anoikis resistance by targeting UBC9 and integrin β3	[22,30]
miR-17/miR-19b	Up-regulated in leukemia stem cells, regulate proliferation by targeting p21	[23]
miR-34	Down-regulated in glioblastomas, regulate cell-cycle or apoptosis by targeting c-MET, Notch-1/2, and CDK6	[24]
miR-181	Up-regulated in hepatic cancer stem cells, maintain stemness by targeting CDX2, GATA6 and NLK	[25]
miR-200 family	Down-regulated in EMT, regulate EMT by targeting ZEB1/2	[26–28]
miR-205	Regulate ZEB1/2 and repress EMT	[26]
miR-29b	Reverse EMT and inhibit invasion in prostate cancer cells	[29]
miR-1	Target Slug to inhibit EMT in prostate adenocarcinoma cells	[31]
miR-15b	Down-regulated in chemotherapy induced EMT, synergistically regulate chemoresistance and invasion with miR-200b by targeting BMI1	[32]
miR-21	Target PTEN to promote EMT and cancer stem cell characteristics	[34,35]
miR-106b-25	Target SMAD7 to induce EMT in TGF-β treated breast cancer cells	[36]
lncRNA		
HOTAIR	Up-regulated in metastatic breast tumors, indicate poor prognosis, enhance metastasis by modulating chromatin state	[40,41]
MALAT1	Up-regulated in metastatic lung adenocarcinomas, promote EMT by enhancing ZEB1/2 expression	[42,43]
MEG3	Involved in p53 signaling, suppress cell proliferation	[44–46]
linc-p21	Activated by p53 and mediate p53 induced apoptosis	[47]
lncRNA-LET	Down-regulated by hypoxia and mediate hypoxia-induced invasion	[48]
PRNCR1/PCGEM1	Activate androgen-receptor pathway and facilitate castration-resistance in prostate cancer	[49]

codon in the translated sequences, this strategy is not applicable for long non-coding RNA transcripts as the transcripts themselves are the functional units. Other knock-out strategies such as disruption of core promoters of ncRNA genes are complicated by the nature that ncRNAs genes are often associated with protein-coding genes. Furthermore, silencing efficiencies of lncRNAs by siRNAs are often lower than proteins, because lncRNAs often form stable secondary structures that preclude binding of siRNAs to the target sequence. These challenges need to be overcome by developing new strategies to modulate ncRNA expression or building new models for functional studies in future.

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